



Comparison of Hemodynamic Responses During Dynamic Exercise in the Upright and Supine Postures After Orthotopic Cardiac Transplantation

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Abnormal hemodynamic responses during supine exercise have been well documented in orthotopic cardiac transplant recipients. To determine the effect of posture, central hemodynamics were studied in 20 patients during a change from supine to sitting and during graded upright bicycle exercise (group U) and were compared with those of 20 patients matched for age, gender and time from transplantation who were studied after passive leg elevation and during exercise in the supine posture (group S).

Passive leg elevation resulted in a 9% increase in stroke index (34 ± 6 to 37 ± 6 ml/m², $p < 0.001$) and a 10% increase in cardiac index (3.1 ± 0.4 to 3.4 ± 0.5 liters/min per m², $p < 0.001$) in group S patients compared with a 15% reduction in stroke index (34 ± 7 to 29 ± 6 ml/m², $p < 0.001$) and a 9% decrease in cardiac index (3.2 ± 0.6 to 2.9 ± 0.5 liters/min per m², $p < 0.001$) in group U patients on assuming the sitting posture. Likewise, both the pulmonary capillary wedge pressure and right atrial pressure increased significantly (13 ± 4 to 17 ± 8 mm Hg, $p <$

0.001 and 5 ± 3 to 7 ± 3 mm Hg, $p < 0.001$) with passive leg elevation in group S and decreased on sitting (12 ± 6 to 8 ± 5 mm Hg, $p < 0.001$ and 5 ± 3 to 3 ± 2 , $p < 0.001$) in group U. Exercise heart rate was slow to rise in both postures and peak heart rate did not differ significantly in the two groups. Stroke index and cardiac index increased to a greater extent in group U during early exercise and, as a result, were not different in the two groups at peak exercise. However, pulmonary capillary wedge pressure was 69% higher (27 ± 7 versus 16 ± 7 mm Hg, $p < 0.0001$) and right atrial pressure 67% higher (15 ± 5 versus 9 ± 5 mm Hg, $p < 0.0001$) at peak exercise in the supine posture, although the absolute increase was similar in both groups.

The marked increase in ventricular filling pressures during exercise and the differences between supine and upright exercise imply an abnormal left-shifted and steep diastolic pressure-volume relation in the transplanted heart.

(*J Am Coll Cardiol* 1990;16:1367-73)

After cardiac transplantation the hemodynamic responses during supine exercise have been well documented (1-4). Prompt and marked elevation of both right and left ventricular filling pressures has been reported, associated with a somewhat less than normal increase in cardiac output at peak exercise (1,5). These observations have been attributed to the effects of cardiac denervation, a mismatch of donor and recipient cardiac size, myocardial fibrosis resulting from rejection and graft vascular disease (1-4,6).

Although observations in the upright posture would be more representative of usual physical activity, the hemody-

namic responses to upright exercise have not previously been reported in heart transplant recipients. To characterize cardiac filling pressures, particularly in the setting of an initially low preload (sitting posture), we studied central hemodynamics during a change in position from supine to sitting and during upright bicycle exercise in 20 healthy orthotopic heart transplant recipients treated with cyclosporine. Results were compared with those of 20 heart transplant recipients matched for age, gender and time from transplantation studied during passive leg elevation and supine bicycle exercise.

Methods

Patient demographics. Patients studied during upright exercise (group U) consisted of 20 survivors (18 men, 2 women) of orthotopic cardiac transplantation. Their mean age was 50 years (range 26 to 63). Twenty patients studied

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Manuscript received January 22, 1990; revised manuscript received May 1, 1990; accepted May 14, 1990.

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during supine exercise (group S) were randomly selected without knowledge of patient identification from a series of patients in whom supine exercise hemodynamics were routinely determined as part of their follow-up after transplantation. Patients from group S (mean 49 years, range 24 to 64) were matched with those in group U on the basis of gender, age and time from transplantation. In both groups 6 patients were studied 3 months after transplantation and 1/4 patients were studied 12 months after transplantation. No patient in either group had evidence of graft rejection that required modification of immunosuppressive therapy at the time of study. Total graft ischemic time was similar for both groups, 214 ± 118 min in group U and 175 ± 75 min in group S ($p = \text{NS}$). Patients in group U had experienced 0.6 ± 0.7 episodes of rejection up to the time of study and those in group S, 0.9 ± 1.1 episodes ($p = \text{NS}$).

Fourteen patients in group U were being treated for hypertension at the time of the study. Six patients were receiving an angiotensin-converting enzyme inhibitor, eight patients were treated with a calcium channel blocker, and six patients were also receiving a diuretic. Similarly, in group S, 13 patients were receiving antihypertensive treatment: 5 with an angiotensin-converting enzyme inhibitor, 5 with a calcium channel blocker and 11 with a diuretic. Antihypertensive medications were not routinely withheld at the time of hemodynamic assessment. All patients gave informed consent for endocardial biopsy and rest and exercise hemodynamic evaluation.

Immunosuppressive therapy. Long-term immunosuppressive therapy consisted of administration of cyclosporine and prednisone in both groups. The mean daily prednisone dose for the whole group of patients under study was tapered from 1 mg/kg body weight perioperatively to approximately 0.2 mg/kg by 3 months and 0.07 mg/kg (usually 5 mg/day) by 1 year. The cyclosporine dose was adjusted to maintain levels of 100 to 200 ng/ml by the whole blood monoclonal radioimmunoassay. Azathioprine was added to the immunosuppressive regimen only if there was steroid-resistant rejection, an abnormal lymphocyte cross match or development of significant renal dysfunction. Twelve patients in group U and 5 patients in group S were being treated with azathioprine at the time of the study.

Hemodynamic measurements. As part of routine assessment, after cardiac transplantation, right ventricular endocardial biopsy was performed through the right internal jugular vein and a flow-directed thermodilution catheter was advanced into a branch of the right pulmonary artery and positioned so that inflation of the balloon with 1 cc of air would result in a satisfactory pulmonary artery wedge pressure tracing. Pressure measurements were obtained with use of Hewlett-Packard 1290 A fluid-filled pressure transducers interfaced with a Hewlett-Packard 8805 D pressure monitoring system. Pressure data were recorded for analysis on heat-sensitive paper with a Hewlett-Packard

7760 A recorder. Pressure transducers were positioned at the level of the midaxillary line for patients studied supine and at the level of the fourth intercostal space at the right sternal border for those studied in the sitting position (3,7). The recorded pressure data included the pulmonary artery (PA) systolic, diastolic and mean pressures; mean pulmonary capillary wedge (PCW) and right atrial (RA) pressures; and arterial blood pressure taken by an automated sphygmomanometer (Dinamap). Mean arterial blood pressure (BP) was calculated with the formula: mean BP = diastolic BP + 1/3 (systolic BP - diastolic BP). Cardiac output (CO) was measured by thermodilution with a Critikon cardiac output computer. Cardiac output measurements were performed in duplicate or triplicate to obtain values in agreement by $\pm 10\%$. Both cardiac output and stroke volume were corrected for body surface area and are reported as the indexes. Systemic vascular resistance (SVR) was calculated with the formula: $\text{SVR} = (\text{mean BP} - \text{RA pressure})/\text{CO}$. Pulmonary vascular resistance (PVR) was calculated with the formula: $\text{PVR} = (\text{mean PA pressure} - \text{PCW pressure})/\text{CO}$.

Exercise protocols. For the supine exercise protocol, baseline hemodynamic measurements were obtained with the patient supine and were repeated with the legs passively elevated on the ergometer: foot pedals. Exercise was begun at a 25 W work load. The work load was increased an additional 25 W every 3 min until exercise was terminated at the point of fatigue. After 2 min in each exercise stage, hemodynamic measurements were repeated in the following sequence: pulmonary artery phasic and mean pressures, mean pulmonary artery wedge pressure, right atrial phasic and mean pressures and cardiac output. The heart rate was recorded at the time of cardiac output determination. Hemodynamic measurements were repeated 2 to 3 min after completion of the exercise protocol with the feet extended upward.

For the upright exercise protocol, baseline hemodynamic measurements were obtained with the patient supine and again in the sitting position with the feet on the upright bicycle ergometer pedals. The exercise protocol thereafter was identical to that described earlier, including hemodynamic measurements.

Data analysis. Data are expressed as mean values ± 1 SD. The highest exercise stage attained by each patient was defined as peak exercise. Within each group hemodynamic changes that resulted from a change in posture (legs down to legs up or supine to sitting) were assessed by two-tailed paired t testing. Likewise, within each group, changes from baseline to each exercise stage were evaluated by two-tailed paired t testing. Differences between groups were assessed by two-tailed unpaired t testing. A p value < 0.05 was considered significant.

Table 1. Hemodynamic Responses to Postural Change and Exercise in 40 Transplant Recipients

	Study Group	Baseline (supine)	Leg Elevation Versus Sitting	Stage 1	Stage 2	Peak	Recovery
Heart rate (beats/min)	Group S	93 ± 13	93 ± 13	100 ± 13	112 ± 16	125 ± 16	112 ± 12
	p value*	NS	NS	NS	NS	NS	0.05
	Group U	95 ± 13	101 ± 12*	108 ± 14	113 ± 13	129 ± 13	120 ± 12
Mean arterial blood pressure (mm Hg)	Group S	113 ± 10	115 ± 14	120 ± 13	124 ± 13	129 ± 11	117 ± 13
	p value	NS	NS	0.03	NS	0.01	NS
	Group U	114 ± 14	112 ± 14	110 ± 12	116 ± 13	119 ± 12	109 ± 12
Cardiac index (liters/min per m ²)	Group S	3.1 ± 0.4	3.4 ± 0.5*	4.1 ± 0.6	5.0 ± 0.6	6.1 ± 1.4	4.3 ± 0.5
	p value	NS	0.005	NS	NS	NS	0.001
	Group U	3.2 ± 0.6	2.9 ± 0.5*	4.2 ± 0.7	4.8 ± 0.8	5.9 ± 1.1	3.5 ± 0.8
Stroke index (ml/m ²)	Group S	34 ± 6	37 ± 6*	41 ± 8	45 ± 9	49 ± 12	39 ± 6
	p value	NS	0.0002	NS	NS	NS	0.0001
	Group U	34 ± 7	29 ± 6*	39 ± 8	43 ± 9	46 ± 10	29 ± 6
Mean PA pressure (mm Hg)	Group S	20 ± 6	24 ± 7*	30 ± 8	35 ± 8	39 ± 8	27 ± 8
	p value	NS	NS	NS	NS	NS	NS
	Group U	21 ± 6	20 ± 6	29 ± 7	30 ± 8	35 ± 10	25 ± 7
Mean PCW pressure (mm Hg)	Group S	13 ± 4	17 ± 8*	22 ± 7	25 ± 8	27 ± 7	16 ± 7
	p value	NS	0.0001	0.0002	0.0001	0.0001	0.0001
	Group U	12 ± 6	8 ± 5*	13 ± 6	15 ± 7	16 ± 7	8 ± 4
Mean RA pressure (mm Hg)	Group S	5 ± 3	7 ± 3*	11 ± 4	13 ± 5	15 ± 5	7 ± 4
	p value	NS	0.0001	0.0001	0.0001	0.0001	0.006
	Group U	5 ± 3	3 ± 2*	6 ± 4	8 ± 5	9 ± 5	4 ± 4
PVR (Wood units)	Group S	1.4 ± 0.9	1.3 ± 0.8	1.2 ± 0.6	1.0 ± 0.5	1.1 ± 0.5	1.4 ± 0.6
	p value	NS	0.002	0.0004	0.001	0.007	0.0001
	Group U	1.6 ± 0.6	2.2 ± 0.8*	1.9 ± 0.6	1.7 ± 0.7	1.8 ± 0.8	2.5 ± 0.9
SVR (Wood units)	Group S	19.2 ± 3.7	18.2 ± 4.3†	15.0 ± 3.5	12.4 ± 2.5	10.7 ± 3.0	14.1 ± 2.6
	p value	NS	NS	NS	NS	NS	NS
	Group U	17.9 ± 3.6	19.9 ± 4.8†	13.0 ± 3.4	11.4 ± 2.7	9.7 ± 2.1	15.7 ± 3.6

*p < 0.001 versus supine; †p < 0.01 versus supine. Data are mean values ± 1 SD. In group S (n = 20) hemodynamics were measured supine, with passive leg elevation and during supine exercise; in group U (n = 20) hemodynamics were measured supine, while sitting and during upright exercise. PA = pulmonary artery; PCW = pulmonary capillary wedge; PVR = pulmonary vascular resistance; RA = right atrial; SVR = systemic vascular resistance.

Results

Exercise duration. The mean exercise duration for group S patients was 9.6 ± 3.0 min (range 6 to 18). Two stages were completed by 4 patients; three stages by 11, four stages by 3 and five and six stages by 1 patient each. Among group U patients the mean exercise duration was 10.1 ± 3.0 min (range 3 to 15). One stage was completed by 1 patient, two stages by 3 patients, four stages by 10 and five stages by 1.

Rest hemodynamics. There was no significant difference between groups with respect to any of the hemodynamic variables at rest (Table 1). Systemic hypertension was prevalent in both groups. Seventy percent of patients in group S and 75% of patients in group U had a supine rest blood pressure > 140/90 mm Hg.

Postural changes (Table 1). Passive leg elevation resulted in a significant increase in cardiac index and stroke index and all central pressures increased slightly but significantly. The heart rate did not change significantly. A change in posture from supine to sitting erect on the bicycle ergometer resulted in a significant decrease in cardiac index and stroke index as well as in a significant decrease in central pressures and also

resulted in a significant increase in rest heart rate (Fig. 1). In group U patients a modest but significant relation between the postural drop in pulmonary capillary wedge pressure and the initial supine rest value was documented (Fig. 2). A similar relation was observed between the extent of postural decrease in right atrial pressure and the supine rest right atrial pressure ($r = 0.53$, $p = 0.02$).

Exercise responses (Table 1, Fig. 1). Heart rate increased slowly in both groups of patients and was similar at peak exercise. A greater increment in the stroke index was observed among group U patients during the first stage of exercise (+34% versus +11% in group S). By peak exercise, however, there was no difference between groups. Likewise, although a greater change in cardiac index was observed among group U patients during the first stage of exercise, peak cardiac index was not significantly different. Among group U patients pulmonary wedge pressure increased immediately with exercise, continued to rise throughout exercise and fell promptly after termination of exercise. The direction and extent of the changes were similar in the two exercise groups; however, the absolute values in the upright

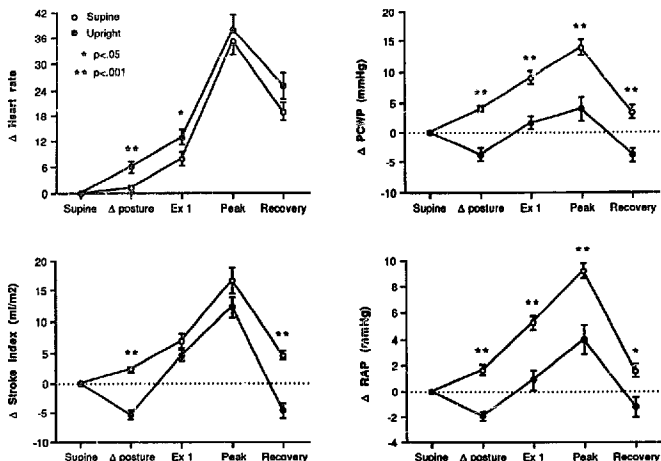
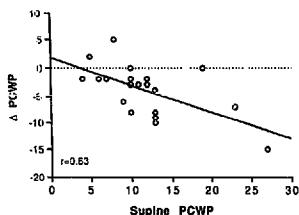


Figure 1. Absolute change (mean values \pm SD) in hemodynamic variables resulting from τ change (Δ) in posture (supine to sitting versus \log elevation) and during dynamic bicycle exercise. Ex1 = exercise stage I, PCWP = pulmonary capillary wedge pressure, RAP = right atrial pressure.

posture were significantly lower at each exercise stage and during recovery in group U compared with group S patients. Similar marked absolute increases in right atrial pressure were noted during exercise end, again, values among group

U patients were significantly lower at each exercise stage. Pulmonary artery pressure was lower in group U patients throughout exercise; the directional change was parallel in the two groups. The rise in systolic blood pressure was more marked during supine exercise and a slight but significant difference between the two groups was noted at peak exercise (186 ± 16 mm Hg in group S versus 169 ± 25 mm Hg in group U, $p < 0.02$) and persisted during the recovery phase. There was no difference in the diastolic blood pressures.

Figure 2. Relation of the supine pulmonary capillary wedge pressure (PCWP) at rest to the absolute change (Δ) in pulmonary capillary wedge pressure on assuming the sitting position.



Discussion

In this study ventricular filling pressures after cardiac transplantation were found to be significantly lower at rest and during exercise in the upright posture but, as previously reported (3), abnormally high pulmonary wedge and right atrial pressures were documented during supine exercise. The cause of the rise in filling pressures during exercise in transplant patients is not well understood; however, the current observations help to further characterize these abnormalities.

Hemodynamic responses to changes in posture. In normal subjects assuming upright posture results in peripheral venous pooling with a resultant decrease in venous return, stroke volume and ventricular filling pressures. In studies of healthy untrained subjects (7-10), the transition from supine

to sitting position resulted in a 15% to 19% increase in heart rate, a 21% to 40% decrease in stroke volume and a 10% to 26% decrease in cardiac output. In contrast to findings in normal subjects, venous return is relatively independent of postural changes in patients with advanced congestive heart failure (11), presumably because of reduced venous compliance (12,13). In the group of cardiac transplant patients under study, the drop in cardiac index and stroke index on assuming the sitting position was intermediate to that reported for normal subjects and patients with congestive heart failure. We and other investigators (14,15) have found that the impaired vasodilation seen in patients with congestive heart failure is slow to normalize after cardiac transplantation. This abnormality may, in part, be related to physical deconditioning and perhaps to the effect of cyclosporine on vascular reactivity.

Despite complete denervation, assumption of the upright position resulted in a small but significant increase in the heart rate of cardiac transplant recipients. The mechanism of this heart rate acceleration is uncertain. It has been observed (16,17) that subjects who received complete pharmacologic sympathetic and parasympathetic blockade continued to have a 5 to 9 beat/min acceleration of heart rate after a change in posture from supine to upright. With the effect of circulating catecholamines thus abolished, it seems likely that there is an intrinsic cardiac mechanism for cardioacceleration.

Hemodynamic responses to exercise. End-diastolic volume and stroke volume vary little during exercise in the supine posture in normal subjects (5,18-24). In upright subjects, however, the initiation of exercise results in a marked increase in both end-diastolic and stroke volumes (7,13,23-25). During the late stages of exercise the stroke volume does not increase further in the upright posture and absolute values remain lower than with corresponding levels of supine exercise. Because of the somewhat higher heart rate during exercise in the upright position, cardiac output remains comparable during supine and upright exercise. Very few data exist regarding the differences in central exercise hemodynamics in different postures; however, in 10 patients without demonstrable cardiac disease, Thadani et al. (7) found that pulmonary capillary wedge pressure changed very little during exercise and remained significantly lower during upright as compared with supine exercise (6 to 13 mm Hg supine versus 4 to 8 mm Hg upright).

One major difference between normal subjects and transplant recipients is the inability to augment heart rate during exercise. Studies by Sonnenblick et al. (26) during exercise at a constant (paced) heart rate showed that cardiac output and stroke volume increased during exercise and that right ventricular end-diastolic diameter increased. Benichou et al. (27) reported that exercise at a slower constant heart rate resulted in a much higher increase in stroke volume than at higher constant rates. Donald and Shepherd (28,29) showed

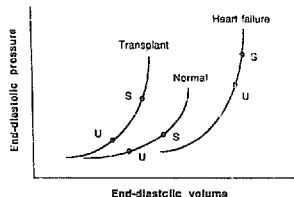


Figure 3. Theoretic end-diastolic pressure-volume relations in normal, failing and transplanted hearts based on current and reported exercise hemodynamic data. S = supine exercise, U = upright exercise.

that augmentation of cardiac output during exercise in denervated dogs was primarily due to an increase in stroke volume. The same mechanism has been found to be operational in heart transplant patients during early exercise (5,30,31). In the supine exercise group under study, the marked increase in both right and left ventricular filling pressures was typical of those previously reported (1-4).

Cardiac compliance after transplantation. The reported studies of cardiac function and exercise hemodynamics in heart transplant patients suggest abnormal cardiac compliance and a ventricular pressure-volume relation shifted leftward (Fig. 3). In several reports (5,30,32) the left ventricular end-diastolic volume of transplant recipients has been shown to be significantly smaller (by up to 30%) than that of supine normal subjects at rest. However, filling pressures at rest are higher in transplant recipients than in normal subjects (3,7,33). During exercise, although end-diastolic volume increases by a greater amount than normal (4,5,30), absolute left ventricular end-diastolic volume remains lower in transplant recipients than in normal subjects, although the reported pressures are clearly higher (3,4). No data exist to allow comparison of cardiac volumes of normal subjects and transplant recipients during upright exercise. However, assuming the end-diastolic volumes during exercise are comparable, the filling pressures in transplant recipients under study were found to be higher than normal (7). Thus, for a given cardiac volume, regardless of posture, ventricular filling pressures are higher than normal in the transplanted heart. Further evidence that suggests abnormal cardiac compliance after transplantation is the finding (Fig. 2) that those patients with higher filling pressures in the supine posture had the greatest decrease in filling pressures on assuming the sitting position, implying cardiac function along a steeper and left-shifted pressure-volume curve (Fig. 3).

Of paramount importance in the cause of the abnormal exercise hemodynamics is the denervated state of the heart

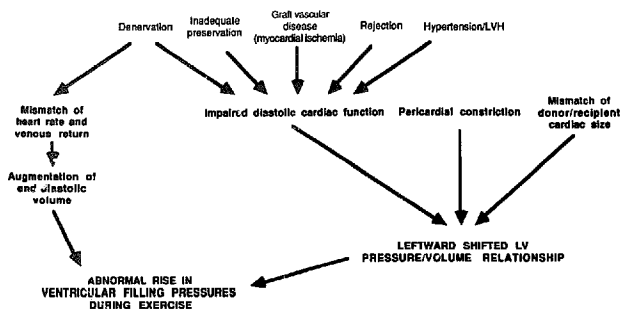


Figure 4. Postulated mechanisms responsible for elevated ventricular filling pressures during exercise in cardiac transplant recipients. LV = left ventricular; LVH = left ventricular hypertrophy.

and blunted heart rate response to exercise. In normal subjects heart rate increases by approximately 35% (5,30) very quickly after the initiation of exercise and the immediate increase in cardiac sympathetic stimulation increases both inotropy and lusitropy (34,35). Because the chronotropic response is impaired in transplanted hearts, the end-diastolic volume, and thus the stroke volume, increases much more than normal to maintain a near normal cardiac output (5,30). As a result, there is a marked *mismatch of heart rate and venous return*. This, in combination with impaired myocardial relaxation resulting from denervation (35), causes ventricular filling pressures to increase immediately with volume loading (3,6) and more markedly during the early stages of exercise (3). As heart rate increases during the later stages of exercise and the end-diastolic volume plateaus (5,30), so do filling pressures. This hypothesis accounts for the presence of abnormal exercise hemodynamics both early and late after transplantation.

Other factors (Fig. 4), may also play a significant role. Graft injury certainly influences hemodynamics early after transplantation and may result in restrictive physiology (36). A mismatch of hearts from a small donor to a large recipient may lead to inadequate preload reserve (4) and in some cases pericardial constraint may also lead to abnormal rest and exercise hemodynamics (3,33). The effects of rejection and small vessel graft vascular disease could also lead to abnormal cardiac compliance. The independent effect of hypertension on cardiac performance could not be determined in this study because most patients were hypertensive and were receiving antihypertensive therapy and therefore could not be compared with a nonhypertensive cohort. We have

previously shown (30) that the radionuclide peak ejection rate at rest is inversely related to mean arterial pressure and probably does influence left ventricular performance. The lower mean arterial pressure at peak exercise in the upright exercise group may therefore have influenced the hemodynamic results.

Another important limitation of this study is the absence of concurrent cardiac volume data. Such data would help to define pressure-volume relations in the transplanted heart more accurately. With the current data only inferences based on published reports can be made. Nevertheless, despite apparent abnormalities of diastolic function, the transplanted heart appears to function in a near-normal manner in terms of left ventricular pressure-volume relation during exercise in the upright posture, resulting in favorable hemodynamics and thereby in the excellent functional capacity of most cardiac transplant recipients.

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